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PREPARATION AND EVALUATION OF COLON TARGETED INDOMETHACIN MATRIX TABLET

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ABSTRACT

Matrix tablets of Indomethacin were prepared by wet granulation method. Guar gum as a carrier, 10% starch paste, HPMC, citric acid and the mixture of talc and magnesium stearate at 2:1 ratio were used. Coating was carried out by using 10% Eudragit L 100. All the prepared formulations were evaluated for hardness, drug content uniformity, stability study and were subjected to *in vitro* drug release studies in rat caecal contents. The highest *in vitro* dissolution profile at the end of 24 h was shown by IF6 followed by IF7, IF8. The other formulation IF4, IF3, IF2 and IF1 were failed to target in colon and these formulation releases the majority of drug within 10 h of study. It may be due to the less proportion of guar gum to retard the drug release. The colon targeted matrix tablet of Indomethacin showed no change either in physical appearance, drug content or in dissolution pattern after storage at 30˚ C/ 65±5 % RH for 2 months.

Key words: Colon targeted, Eudragit L-100, Guar gum, Indomethacin, Matrix tablets, Rat caecal content.

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INTRODUCTION

Current literature survey indicates that the considerable amount of stress has been paid for tailoring colon targeting of drugs for diverse significance. In the colon, both confined and systemic delivery of drug can take place[1,2]. A local factor of drug delivery could allow topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or crohn's disease[3, 4, 5]. Such inflammatory conditions are usually treated with glucocorticoids[6] and sulfasalazine. The treatment might be effectually if the drug were targeted precisely to the site of action in the colon. Site-specific drug delivery could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of gastrointestinal tract[7].

The orally administered drugs acting to the colon target depend on pH-dependent polymers and the utilization of carriers[8, 9]. They are assumed to remain within the physiological environment of stomach and small intestine, but undergo erosion in the colonic region as result of degradation by bacterial population. Various polysaccharides such as guar gum, inulin, pectin, cellulose, chondroitin sulphite, chitosan etc. are being employed for colon targeting[10, 11, 12].

In the present work, we have chosen a non steroidal anti inflammatory drug, indomethacin as a model drug[13, 14]. The tablets were prepared using guar gum alone in different concentrations with other polymers and these tablets were evaluated for their ability to remain intact in stomach and small intestine and release the majority of drug in colon.

MATERIALS AND METHODS:

Indomethacin was obtained as gift sample from Reddy's Laboratories, Hyderabad. Guar gum, Magnesium stearate, Purified Talc, HPMC, Citric acid powder and PEG-4000 were purchased from S.D. Fine chemicals, Mumbai. Starch obtained from Smith and Kenner Pharmaceuticals and Eudragit L-100 obtained from Mahendra Labs Pvt Ltd, Bangalore.

Preparation of colon targeted matrix tablets of indomethacin:

Matrix tablet of Indomethacin were prepared by the wet granulation technique[15] using 10 % starch paste. HPMC was used as diluent, an organic acid citric acid was added in matrix granules to regulate pH locally and retard the dissolution of enteric polymers in granule cores and their enteric coatings and the mixture of talc and magnesium stearate at 2:1 ratio was used as lubricant. The composition of different matrix formulation used in the study containing 10 mg of Indomethacin was described in Table 1. In all the formulation guar gum is mixed with Indomethacin and HPMC. The powder were blended and granulated with 10% starch paste. The wet granules were dried at 50 ºC for 2 h. The dried granules were lubricated with a mixture of

talc and magnesium stearate (2:1). The lubricated granules were compressed at compression force 4-6 kg using 8 mm flat punch on tabletting machine. The tablets were coated with a 10% w/v solution of Eudragit L-100, using a pan coating equipment. PEG-4000 (1% w/v) was used as a plasticizer. The percent weight increase of each group of formulation of tablets after coating varied between 2.0 ± 0.005% w/w.

Table 1 -Different formulation of colon targeted matrix tablet

Formulation Code	Indomethacin (mg)	Guar gum		HPMC E50LV		Starch (mg)	Citric Acid (mg)	Magnesium Stearate (mg)	Talc (mg)
		(%)	(mg)	(%)	(mg)				
IF1	10	7.5	18.75	62.5	156.25	25	25	5	10
IF2	10	15	37.25	55	137.5	25	25	5	10
IF3	10	22.5	56.25	47.5	118.75	25	25	5	10
IF4	10	30	75	40	100	25	25	5	10
IF5	10	37.5	93.75	32.5	81.25	25	25	5	10
IF6	10	45	112.5	25	62.5	25	25	5	10
IF7	10	52.5	131.25	17.5	43.75	25	25	5	10
IF8	10	60	150	10	25	25	25	5	10

Uniformity of drug content study:

The matrix tablets of Indomethacin were tested for their drug content using 20 tablets. Quantity of the powder equivalent to 10 mg of Indomethacin was weighed and dissolved in ethanol and diluted further to estimate drug concentration using UV-Spectrophotometer at 320 nm.

Measurement of swelling index:

Swelling index was found out using 10 ml of phosphate buffer at pH 7.4. The tablets were removed at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h. Excess water was removed using filter paper. The swollen tablets were reweighed and the swelling index of each tablet was calculated using the following equation.

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

Drug-excipient compatibility study:

Pure drug and prepared formulations were tested for compatibility study using IR spectrophotometer. It was found that the prepared formulations were compatible with the drug and the polymer.

Drug release studies

1. Preparation of rat caecal contents:

To assess the susceptibility of guar gum, drug release study was carried out in presence of rat caecal content because of the similarity with human intestinal flora[16]. In order to induce enzymes specially acting on guar gum in the caecum, male albino rats weighing between 150-200 g, maintained on normal diet were incubated with Teflon tubing and 1 ml of 4% dispersion of guar gum in water was administered into the stomach for 7 days. Thirty minutes before the commencement of drug release studies, six rats were killed by spinal traction. The abdomen were opened, the caecal bags were isolated, legated at both ends and cut loose and immediately transferred in to phosphate buffer, previously bubbled with CO_2. Then the caecal bags were opened, their contents were individually weighed, pooled and then suspended in phosphate buffer to give a final caecal dilution of 4% w/v.

2. Dissolution study:

In vitro drug release study was conducted at 37 ºC and 100 rpm for 2 h in 900 ml buffer of pH 1.2. The dissolution medium was replaced with 900 ml of pH 7.4 phosphate buffers and tested for drug release up to 3 h. Drug release was continued in phosphate buffer containing 4% (w/v) rat caecal matter up to 24 h[8]. 5 ml of sample was withdrawn at different time intervals, subjected for centrifugation and the drug content was estimated using UV-spectrophotometer at 320 nm.

RESULTS AND DISCUSSION:

In this investigation, various formulations of colon targeted matrix tablet of indomethacin were prepared by wet granulation technique in different proportions of guar gum as carrier and coated with Eudragit L-100 to target the model drug to the region of colon.

In order to select the best formulation, various parameters were checked and subjected to *in vitro* dissolution studies, and their release profile was observed and compared with other formulation. Evaluation of physicochemical parameters such as appearance, bulk density, percentage compressibility, weight variation, friability, drug content and *in vitro* dissolution studies were performed. Stability studies were performed for a six month as per ICH guidelines and parameters like physical appearance, drug content uniformity, and *in vitro* dissolution studies of the formulations were assessed.

The drug was compatible with the formulated ingredients, which was identified by IR data. Flow property, thickness, hardness, friability and weight variation test were within the limit (Table 2). Good and uniform drug content (>98) was observed within the batches of different tablet formulation.

Table 2- Evaluation data for prepared indomethacin colon targeted matrix tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Swelling index	Percentage drug released at 24 h in the presence of rat caecal contents	Correlation coefficient (Higuchi) (r^2)
IF1	5.9±0.115	0.1 ± 0.01	98.85 ± 0.0664	--	--	--
IF2	6.5±0.288	0.12 ± 0.04	99.51 ± 0.0721	--	--	--
IF3	5.7±0.172	0.12 ± 0.02	97.60 ± 0.0321	--	--	--
IF4	5.9±0.152	0.12 ± 0.08	98.14 ± 0.0264	--	--	--
IF5	6.8±0.155	0.1 ± 0.01	98.42 ± 0.0529	2.0431	--	--
IF6	6.2±0.115	0.08 ± 0.03	98.79 ± 0.0503	1.6967	97.79±0.98	0.9192
IF7	5.8±0.110	0.12 ± 0.04	99.30 ± 0.0251	3.3101	87.83±1.24	0.8948
IF8	5.8±0.115	0.04 ± 0.01	100.28 ± 0.085	2.7829	79.66±2.04	0.9026

In vitro dissolution studies suggested that the highest *in vitro* dissolution profile at the end of 24 h was shown by IF6 followed by IF7 and IF8.**(**Figure 1**)**The other formulation like IF4, IF3, IF2 and IF1 failed to target the Indomethacin in the colon and these formulation releases the majority of drug within 10 h. It may be due to the less proportion of guar gum, which retard the drug release.

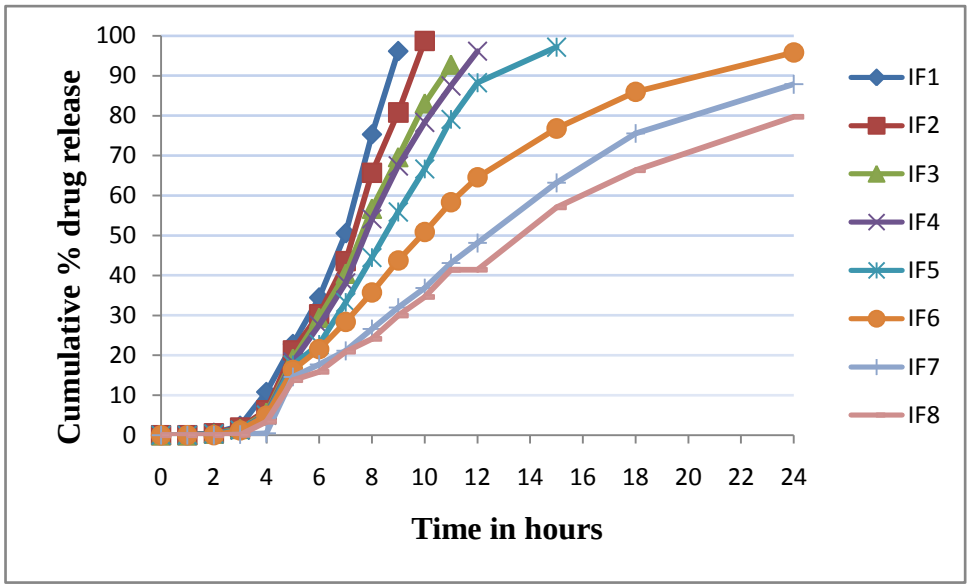

Figure 1: Drug release profile of prepared Indomethacin colon targeted matrix tablet.

From the *in vitro* dissolution studies, it can be discussed that the colon targeted matrix tablet containing 45% guar gum was the best formulation to target the indomethacin in the treatment of colon cancer. Since the drug release from formulations IF6, IF7 and IF8 showed dissolution up to 24 h they were chosen for the investigation of kinetic model.

The selected formulations were subjected to the accelerated stability at 30±2°C / 65±5% RH for 3 months and evaluated for their appearance, hardness, friability, drug content and *in vitro* dissolution studies. There were no significant variations in the appearance, hardness, friability, drug content and *in vitro* dissolution studies. This clearly indicates that the prepared formulation was stable.

CONCLUSION:

From this study, it was concluded that the prepared indomethacin colon targeted matrix tablet has the ability to control drug release over prolonged periods.

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